PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/027231	20.08.2004	11.05.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/11, C12P19/34, C07H21/02, C07H21/04, A01N43/04, A61K31/713

Applicant
SIRNA THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 33, 35

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 33, 35

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-32, 34

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32, 34
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-32, 34
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-32, 34
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

1. The present application contains 11 separate groups of inventions as listed in the International Search Report that are not so linked as to form a single general inventive concept.

2. The present application relates to double stranded short interfering nucleic acid (siNA) molecules that direct cleavage of a G protein coupled receptor for asthma susceptibility (GPRA) or of an asthma associated alternatively spliced gene 1 (AAA1) RNA via RNA interference.

3. The technical problem which can be extracted from the disclosure as filed is that of the provision of compounds for the inhibition of the expression of the G protein coupled receptor for asthma susceptibility (GPRA) or of an asthma associated alternatively spliced gene 1 (AAA1).

4. The different solution for the technical problem as presented in the specification are siNA molecules that direct cleavage of a G protein coupled receptor for asthma susceptibility (GPRA) RNA via RNA interference which are described as such, siNA molecules directing the cleavage of the G protein coupled receptor for asthma susceptibility (GPRA) or of an asthma associated alternatively spliced gene 1 (AAA1) that are defined by their sequence and such siNA molecules defined by their sequence and which are chemically modified.

5. The particular solution for the technical problem presented by **invention 1** are siNA molecules as such that direct cleavage of an G protein coupled receptor for asthma susceptibility (GPRA) RNA via RNA interference.

The particular solutions for the technical problem presented by **inventions 2-4** are specific siNA molecules directing cleavage of an G protein coupled receptor for asthma susceptibility (GPRA) RNA defined by their sequence.

The particular solution for the technical problem presented by **invention 5** are specific siNA molecules directing cleavage of an G protein coupled receptor for asthma susceptibility (GPRA) RNA defined by their sequence wherein said siNAs are chemically modified.

The particular solutions for the technical problem presented by **inventions 6-10** are specific siNA molecules directing cleavage of an asthma associated alternatively spliced gene 1 (AAA1) RNA defined by their sequence.

The particular solutions for the technical problem presented by **inventions 11** are specific siNA molecules directing cleavage of an asthma associated alternatively spliced gene 1 (AAA1) RNA defined by their sequence wherein said siNAs are chemically modified.

6. The common concept of the different particular solutions for the technical problem presented by the inventions 1-5 and 6-11 are siNA molecules that direct cleavage of an RNA via RNA interference of a gene involved in asthma. Such a concept is, however, known from D1 and D2.

7. Thus, the groups 1-5 and groups 6-11 of inventions are not so linked as to form a single general inventive concept and the present application, therefore, lacks unity (lack of unity a posteriori, Rule 13.1. PCT).

8. In addition, the different specific siNAs described in the present application for the solution of the technical problem are structurally completely different and do not share a special technical feature (see PCT International Search and Preliminary Examination Guidelines, 10.17(a) and 10.52-10.57). Said specific siNAs, therefore, are not so linked as to form a single general inventive concept (lack of unity a priori, Rule 13.1. PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The documents mentioned in the present Written Opinion / International Preliminary Examination Report are numbered as in the International Search Report. D1 corresponds to the first document of the Search Report, D2 to the second document etc.

The documents D1 or D2 can be regarded as closest prior art to the subject-matter of the present application and shows siRNA molecules directing cleavage of the RNA of a gene involved in asthma.

The subject-matter of the present claim differs from D1 or D2 in that siNA molecules directing cleavage of the RNA of the G protein coupled receptor for asthma susceptibility (GPRA) gene is described.

The subject-matter of claims 1-32, 34 is therefore acknowledged as being new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as providing compounds that inhibit the expression of an alternative gene involved in asthma.

The solution to this problem proposed in claim 1 is considered as involving an inventive step (Article 33(3) PCT) since the prior art does not contain any indication that would prompt the skilled person to provide siNA molecules directing cleavage of the RNA of the G protein coupled receptor for asthma susceptibility (GPRA) gene.

Claims 2-32, 34 are dependent on claim 1 and as such are also acknowledged as meeting the requirements of the PCT with respect to inventive step.

Re Item VIII
Certain observations on the international application

Arts. 5 and 6 PCT

A G protein coupled receptor for asthma susceptibility (GPRA) is not known in the prior art at the priority date claimed. Also the present application does not disclose said receptor. The subject matter of claims 1-32 and 34 is, therefore, not sufficiently disclosed or supported contrary to Arts. 5 and 6 PCT.

The attention of the applicant is drawn to the fact that a reply to this opinion is only expected if he intends to file a chapter II demand.